REMARKS

Reconsideration of the above-identified application in view of the remarks following is respectfully requested.

Claims 23, 24, 28-33, 35, 40, 42-46, 48-52, 54-56 and 59-83 are in this case. Claims 23, 24, 28-33, 35, 40, 42-46, 48-52, 54-56 and 59-83 have been rejected. Claims 25-27, 32, 34, 36-42, 45-48, 51-54, 57-58, 61-67 and 72-83 have now been canceled. Claims 23, 24, 28-31, 33, 35, 43, 44, 49-50, 55-56, 59-60 and 68-71 have been amended. New claims 84-100 have now been added.

Double Patenting

Applicant will allow U.S. Patent Application No. 10/399,715 to go abandoned by failure to respond to the Office Action dated April 21, 2006. Therefore no terminal disclaimer will be filed as part of this response.

35 U.S.C. § 112 First Paragraph

The Examiner has rejected claims 23, 24, 28-33, 35, 40, 42-46, 48-52, 54-56 and 59-83 as failing to comply with the enablement requirement. The Examiner's rejections are respectfully traversed. Claims 25-27, 32, 34, 36-42, 45-48, 51-54, 57-58, 61-67 and 72-83. Claims 23, 24, 28-31, 33, 35, 43, 44, 49-50, 55-56, 59-60, 68-71 have been amended. New claims 84-100 have now been added.

The Examiner states that given the unpredictability in the ex vivo gene therapy art, and further given that the specification fails to provide specific guidance on which nucleic acids encoding which protein can be used to treat a specific disease, the skilled artisan would have been required to engage in undue experimentation to develop a method within the scope of the claims for treating any disease. In a telephone interview graciously granted by the Examiner, Applicant presented recently obtained experimental data which supports the scope of the claimed invention.

Specifically, the Examiner states that the specification does not provide any working examples with regard to the treatment of a diseased animal by implantation of cells as recited in the claims. The Examiner states that the declaration of Dr. Yair Feld filed March 3, 2003 describes in vivo assay for prolonging the effective refractory period (ERP) in rats administered with Kv1.3 expressing fibroblasts.

However, the Examiner contends that the animals used in the experiments were healthy animals and therefore no treatment was noted.

Applicant wishes to draw Examiner's attention to additional results obtained by the present inventors, as well as by others, showing treatment of a variety of cardiac and neuronal indications while using the teachings of the present invention (see attached Appendices A and B as well as declaration; and a paper by Potapova et al. 2004 Circulation Research 952-959). These results provide ample support for the treatment of a variety of cardiac and neuronal indications using a number of cells, ion channels and construct systems in well-known animal models (diseased animals, from which treatment may be directly inferred, discussed in page 29 line 15 of the instant application), thus supporting the scope of the claimed invention.

For Examiner's convenience, these results are summarized in the following table.

Tissue	*Indication*	*Support*	*Animal Model*	*Cells*	*Channel*
Cardiac	1. Atrial Fibrillation 2. Ventricular Tachycardia	Appendix A	Pig	Fibroblasts	Kv1.3 H401W Kir 2.1
	Pacemaking	Potapova et al. (2004)	Dog	Human Mesenchymal Stem Cells	HCN
Neuronal	Parkinson's Disease	Appendix B	Rat	Fibroblasts	Kv1.3 H401W Kir 2.1

Briefly, Appendix A shows the ability of three different human fibroblast populations (NIH 3T3) each exogenously expressing a different potassium channel (WT Kv1.3, Kv1.3 H401W or Kir2.1, described in page 6 first paragraph of the instant application) to in *vivo* prolong the ERP in the ventricles during ventricular tachycardia induced by rapid pacing, and in the AV node of domestic pigs administered with the cells (see Figure 3 of the attached Appendix A). These results strongly support the claimed invention for treating ventricular tachycardia.

Treating is further established in another animal model of atrial fibrillation. Acute atrial fibrillation was induced in two domestic pigs by burst atrial pacing

[Donahue JK, Heldman AW, Fraser H, McDonald AD, Miller JM, Rade JJ, Eschenhagen T, Marban E. Focal modification of electrical conduction in the heart by viral gene transfer. Nat Med. 2000 Dec;6(12):1395-8, attached]. As shown in Figure 5 of the attached Appendix A, administration of Kv1.3 H401W-expressing NIH 3T3 to the pigs reduced the ventricular response by nearly half. Thus, these results strongly support the claimed invention for treating atrial fibrillation.

Potapova et al. injected indiscriminate ion channel-(i.e., HCN2, mentioned in Page 2, line 18 of the instant application) expressing mesenchymal stem cells *in situ* to the left ventricular wall of canine's heart. Bradycardia was induced by left and right vagal stimulation until escape pacemaker function occurred. These results strongly support the use of the present invention for pacemaking.

Thus, the above results, which are based on the teachings provided in the instant application, clearly support the methods of the present invention for the treatment of cardiac diseases and in particular treatment of atrial fibrillation, ventricular tachycardia and pacemaking.

Additional results obtained by the present inventors and shown in the attached Appendix B illustrate the ability of Kv1.3 expressing fibroblasts to improve the asymmetric rotation behavior of a rat model for Parkinson (6-ODHA lesioned rats, see Tables 2 and 3 and Figure 8 of Appendix B), clearly pointing to the therapeutic effect in Parkinson model. These results are well supported by the instant application in which Applicant foresaw the potential use of cells expressing potassium channels in the treatment of CNS disorders (see Table 3 Page 47 of the instant application).

Thus, these results strongly support the methods of the present invention for the treatment of neuronal disorders such as Parkinson's disease.

Taking into consideration that the underlying mechanism of the diseases of the present invention is a pathological alteration in an excitable tissue region, it is Applicant's strong opinion that other cardiac and neuronal indications which may be alleviated by modifying the electrophysiological function of the excitable tissue are also enabled.

Notwithstanding the above and in order to expedite prosecution, Applicant has elected to limit claims 23, 28, 29, 33, 35 and add new independent claims 84, 87and

90 such that they are limited to the treatment of the diseases which are directly supported by the present results.

The Examiner further states that the specification fails to provide any specific guidance on the generation of the nucleic acid construct to be used in the gene therapy method for the treatment of any specific disease or disorder.

Applicant wishes to draw Examiner's attention to a detailed description of nucleic acid constructs which may be used by the present invention (see Pages 24-26 of the instant application).

Thus, the instant application teaches single promoter (IRES mediated) or double-promoter expression construct. Alternatively taught are expression systems (which include more than one nucleic acid vector). Expression constructs of the present invention may be constitutive or inducible constructs and may include additional regulatable elements. Also the promoters which may be used are varied such as the constitutive promoters exemplified by CMV promoter of the pCDNA3 construct (see page 26 line 8) and the EF-1 alpha promoter of pEF/myc/cyto. Alternatively, inducible promoters such as of the pTRES (tet-inducible) listed in page 26 line 7 of the instant application may be used. References to the major molecular vendors are provided. Thus, it is Applicant strong opinion that the generation of expression constructs which may be used in accordance with the present invention are well supported.

Applicant wishes to further note that the examples of the constructs provided in the instant application, indeed well anticipated the successful use of these constructs in alleviating disease. For example, the pIRES2 which was used to express the H401W (in vivo results are presented in Appendix A and B) as well as HCN2 channel (see Potapova et al. page 953 "Materials and Methods") was obtained from Clontech (referenced in Page 26, line 8 of the instant application).

Alternatively, the pRC/CMV which was used to express the Kv1.3 or Kir2.1 (see Appendix A) is available from Invitrogen (catalog number V75020, referenced in page 26 line 6 of the instant application).

Thus, it is Applicant strong opinion that numerous nucleic acid constructs which can work *in vivo* are fully enabled by the instant application and the skilled

artisan will be able to readily select the optimal promoter sequence using the above described in vitro and in vivo assays, without resorting to undue experimentation.

The Examiner further notes that the field of treating cardiac arrhythmias as a whole using gene therapy is unpredictable, specifically mentioning the inability to control the duration and the level of gene expression.

Applicant wishes to note that in sharp contrast to sporadic reviews which criticize the use of cell therapy for the treatment of cardiac diseases, a reasonable search of the web uncovers numerous successful cell therapy experiments for the treatment of the diseases encompassed by the claimed invention. An example for such is attached ("Stem Cell Therapy Symposium Heinrich Heine University" outlines clinical results obtained by cell based therapy).

Moreover, the general use of ex-vivo gene therapy for neurodegenerative disorders has been successfully implemented in clinical trials [Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J.A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med. 2005 May;11(5):551-5. Epub 2005 Apr 24, attached].

In many cases, the unpredictability of an art lies not with the technique but rather with other factors, which at times are either unknown to the scientist or are uncontrollable thereby.

For example, chemotherapy is a widely used pharmacological technique for treating cancer. The effects of chemotherapy on cancer treatment cannot be predicted since it is influenced by parameters associated with the patient and/or the disease. As a result of its unpredictability, many of the patients treated do not actually benefit from chemotherapy, a fact which has not led to dismissal of this technique.

Thus, although difficulties in utilizing cell-therapy technology as well as numerous other widely utilized molecular techniques have been reported in the art, successful implementation of these so called "unpredictable" techniques has been reported in numerous publications including patent publications which disclose treatment methods utilizing cell-therapy (including Donahue's himself, see U.S. Pat. No. 6,992,070). In fact, Donahue states that pre-clinical efficacy should be monitored prior to resorting to human studies (see page 222 right column of Donahue 2005a).

Such experiments were indeed effected by the present inventors and others (see above) increasing the predictability levels of the present invention.

The Examiner further states that the success of the protocol of the instantly claimed method is critically dependent on matching a given disease with an appropriate therapeutic construct and an appropriate cell type.

However, this is clearly not correct, as the results presented here and summarized in the table above clearly show the different nucleic acid constructs expressing different genes introduced to different cell types may be used for the treatment of various diseases encompassed by the claimed invention.

Thus, it is Applicant strong opinion that the invention as now claimed is fully supported and enabled.

In view of the above arguments and amendments, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 112 First Paragraph

The Examiner rejected claims 64-84 as being indefinite in their recitation of "said cells" because the term has ambiguous antecedent basis

Claims 23, 28, 29 and 33 have now been amended such that the implanted cells are better defined as those which are genetically manipulated and therefore may form a gap junction with the cells of the tissue (host) to thereby overcome the Examiner's rejection with respect to these claims.

In view of the above amendments and remarks it is respectfully submitted that Claims 23, 24, 28-31, 33, 35, 43, 44, 49-50, 55-56, 59-60, 68-71 and 84-100 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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July 6, 2006

Enclosed:
Inventor Declaration
Inventor CV
Appendix A
Appendix A Figures
Appendix B
Appendix B Figures
Reference - Potapova et al
Reference - Donahue et al.
Reference - Stem Cell Therapy Symposium
Reference -Tuszynski et al.